Medical Staff Conference

Familial Colonic Cancer Syndromes

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *The topic of this conference is inherited colonic cancer syndromes. It will be presented by Dr Richard Boland.*

Dr Boland received his medical degree from Yale and his house-staff training at St Francis Hospital in Hartford, Connecticut. He had further clinical experience in the Indian Health Service and at the Public Health Service Hospital here in San Francisco. After the completion of a fellowship in gastroenterology at the University of California, San Francisco, he joined the faculty as an assistant professor of medicine in gastroenterology at the Veterans Administration Medical Center.

DR BOLAND:† This discussion will focus on the familial colonic cancer syndromes. Cancer of the colon and rectum is very common in the Western countries and can be expected to develop in 5% of the population of the United States. The pathogenesis of most of these cancers is related primarily to environmental factors, since the incidence is highly variable worldwide. Furthermore, in population groups at low risk for the disease such as in Japan, a higher risk develops when they migrate to endemic regions such as North America. Not everyone, however, in any given population group is equally susceptible to the environmental factors responsible for colonic cancer. This malignancy is three to four times more likely to develop in first-degree relatives of patients with cancer of the colon (even excluding those with polyposis coli) than in persons from the general population.[1] At least part of this increased risk may be due to discrete familial cancer syndromes.

There are two general categories into which persons who have the familial colonic cancer syndromes may be divided, those with and those without antecedent polyposis. These two categories may be further subdivided into clinically distinct but closely related syndromes. There is strong experimental evidence that provides a common pathogenetic basis for the polyposis syndromes, and additional lines of investigation that suggest unifying links between some of the polypotic and nonpolypotic colon cancer syndromes, despite the fact that they are clinically quite different. Pertinent case histories will be presented to illuminate these syndromes, followed by a discussion of the clinical features of each and current areas of research.

The Polyposis Syndromes: Familial Polyposis Coli and Gardner's Syndrome

CASE 1. The patient, a 59-year-old man, had crampy lower abdominal pain and intermittently dark feces. He had no history of gastrointestinal disease except that guaiac-positive tests of stool specimens had been noted for many years (in the absence of anemia), which had been attributed to the excessive use of alcohol and aspirin. There was no history in the family of polyps or cancer of the colon. The patient had no children. On physical examination he had several bony protuberances on his skull and occiput that had been present for more than 25 years (Figure 1). He also had several scars due to previous drainage of sebaceous cysts, and had surgical scars from bilateral axillary adenectomy for hidradenitis suppurativa. There were no soft tissue masses, and the abdominal examination elicited no abnormalities. The stool specimen was brown and guaiac test was positive. Other laboratory studies were unrevealing. On sigmoidoscopy there were multiple small polyps in the rectum and sigmoid colon. A barium enema study showed two large masses that nearly obstructed the transverse colon (Figure 2) and multiple smaller colonic polyps. The small polyps were tubular adenomas and the large masses in the transverse

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colon consisted of a villoglandular adenoma and an invasive adenocarcinoma. The patient underwent an exploratory laparotomy and the large lesions were removed; metastatic disease was found in the liver, however. The specimen of resected colon showed multiple adenomatous polyps (Figure 3). A diagnosis of Gardner's syndrome was made, despite the patient's age and the apparently negative family history.

This case exemplifies several important points that should be made about the closely related disorders, familial polyposis coli and Gardner's syndrome (Tables 1 and 2). Familial polyposis coli is a disease in which several thousand adenomatous polyps may eventually carpet the colon (Figure 4) and carcinoma usually develops if the colon is not removed. The appearance of adenomas antedates the appearance of cancer by about 14 years (Table 3), and it is within this latent period that the premalignant disease should be recognized and treated.[4] The disease is inherited as an autosomal dominant characteristic but, as in our patient, in about 20% of cases, there is a negative family history. At least some of the family histories are spuriously negative because denial of the disease is not uncommon in these families.[5]

Gardner's syndrome has all of the features of familial

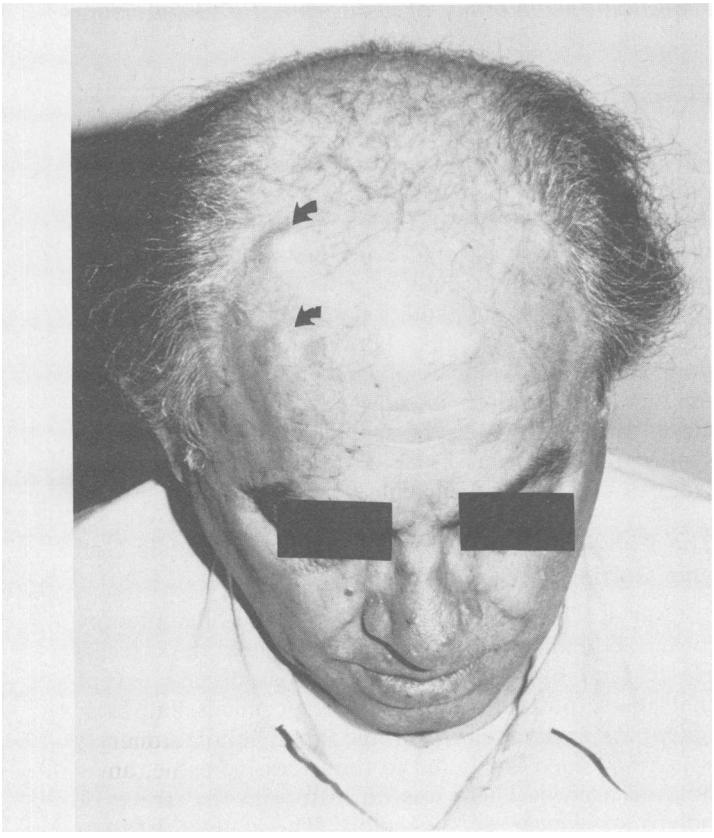

Figure 1.—Arrows show osteomas on the skull of a patient with Gardner's syndrome.

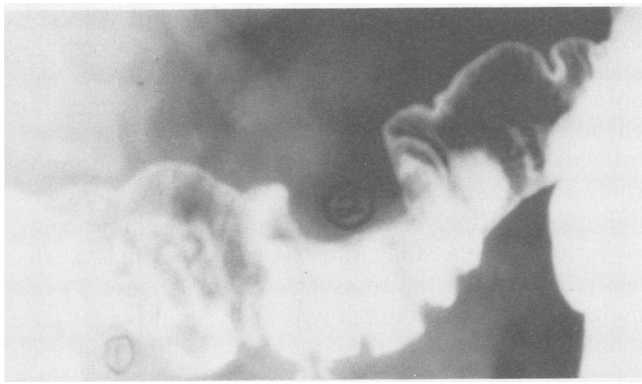

Figure 2.—X-ray film taken during a barium enema study of the patient in Figure 1, showing two large filling defects, numbered (1) and (2) in the transverse colon.

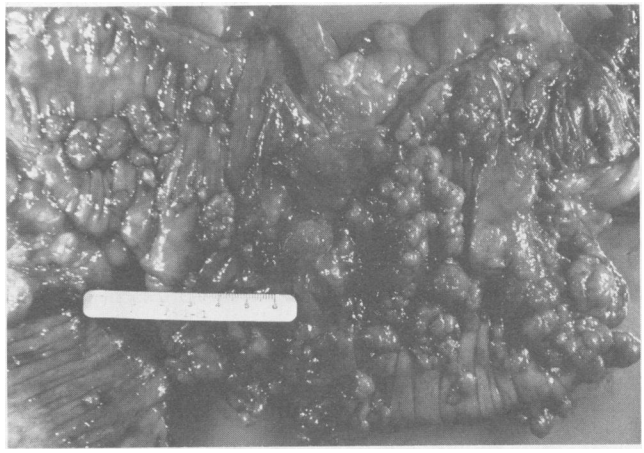

Figure 3.—Resected specimen of ascending colon from the patient in Figures 1 and 2, who had Gardner's syndrome. The specimen shows diffuse colonic polyposis. Most of the polyps were smaller than 5 mm and all were adenomas.

TABLE 1.—*Familial Polyposis Coli*

Characteristic Features
Multiple adenomatous polyps of the colon (up to several thousands)
Autosomal dominant inheritance (20% have negative family histories)
In virtually all colonic cancer develops without colectomy
Polyposis usually begins after puberty; carcinoma typically appears 1 to 2 decades later
Polyps may occasionally occur in the stomach and small intestine (but cancer in these areas is rare)

TABLE 2.—*Gardner's Syndrome*

Characteristic Features
Colonic adenoma and carcinoma similar to that seen in familial polyposis coli
Adenomatous polyps of the small intestine and stomach (other non-neoplastic polypoid lesions are also found in the stomach)
Osteomas, especially of the mandible and cranium
Soft tissue tumors: fibromas, lipomas, sebaceous cysts, epidermoid cysts
Mesenteric fibromatosis (desmoid tumors); may be massive after laparotomy[2]
Dental abnormalities (impacted and supernumerary teeth)
Small intestinal carcinoma (especially periampullary)
Abnormalities of retinal epithelium[3]
Rarely, malignant degeneration of osteomas or soft tissue tumors

polyposis coli, with the addition of a variety of benign soft tissue and bony tumors (Table 2). Patients who have Gardner's syndrome are also at risk for adenomatous polyps and carcinoma of the small intestine, especially in the periampullary region. Polyps are found in the stomach in both syndromes. The gastric lesions have included both adenomas and hamartomatous polyps.[6] To date, cases of gastric carcinoma have been reported in this setting only from Japan, where the general population has a very high incidence of gastric cancer.[7] A number of dental lesions are found in patients with Gardner's syndrome, including mandibular osteomas and impacted or supernumerary teeth. Even when not clinically apparent, a roentgenogram of the mandible will show characteristic lesions in more than 90% of patients.[8] A potentially serious complication is the development of diffuse mesenteric fibromatosis (desmoid tumors) after laparotomy, which can cause gastrointestinal obstruction and prevent additional operative intervention. Mesenteric fibromatosis complicates about 17% of cases of Gardner's syndrome and may occur spontaneously.[2]

In rare instances, osteosarcoma or fibrosarcoma[9] has occurred. Recently, hypertrophy of retinal pigment epithelium has been reported in some, but not all cases of Gardner's syndrome.[3]

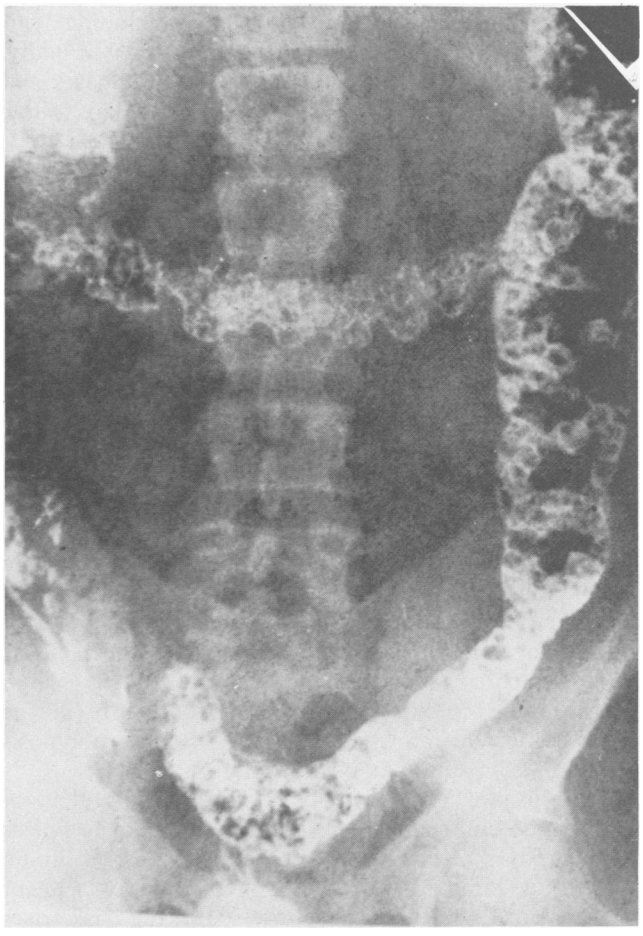

Figure 4.—X-ray film taken during a barium enema study in a patient with familial polyposis coli who had diffuse colonic polyposis showing hundreds of tiny adenomatous polyps.

TABLE 3.—*Natural History of Colonic Polyposis*

Stage	*Mean Age Years*
Appearance of adenomas	24.5
Onset of symptoms	33.0
Diagnosis of adenomas	35.8
Diagnosis of cancer	39.2
Death from cancer	42.0

From Bussey.[4]

TABLE 4.—*Overlap Between Familial Polyposis Coli and Gardner's Syndrome*

Colonic neoplasms (adenomas and carcinomas) develop in a similar time frame in both[4]
Occult mandibular osteomas are found in patients with familial polyposis coli[8]
Gastric and small intestinal polyps are found in patients with familial polyposis coli[6,10,11]
Some affected members in Gardner's syndrome families lack extraintestinal manifestations[12]
Similar abnormalities exist in colonic epithelial cells and cultured skin fibroblasts in both syndromes[13]

Clinical Overlap

The clinical overlap between familial polyposis coli and Gardner's syndrome has led some investigators to suggest that these syndromes may be variable expressions of a single genetic defect (Table 4). Most patients with Gardner's syndrome do not have the full clinical triad of polyposis, soft tissue tumors and bony tumors. In one study of 280 family members at risk for Gardner's syndrome, at least one manifestation of the disease had developed in 126 (45%).[14] Of these, 60% had soft tissue tumors, 32% osteomatosis and 67% colonic polyposis; only 20% had the complete triad. Therefore, only a few patients with Gardner's syndrome have the full spectrum of the syndrome, and the polyposis may be inherited separately from the extraintestinal manifestations.[12] Also, when specifically sought, many typical patients with familial polyposis coli have occult lesions in the mandible,[8] the stomach[6] and the small intestine[10,11] similar to those characteristic of Gardner's syndrome. Finally, both syndromes show similar abnormalities in the regulation of the growth of colonic epithelium and cultured skin cells in vitro (see below).

Glioma-Polyposis Syndrome

A variant of the polyposis syndromes is the glioma-polyposis or Turcot syndrome.[15] Several cases have been reported in which siblings have had colonic adenomatous polyposis and malignant brain tumors. In most of the initial reports, the parents did not have a history of polyposis and the affected persons died of their brain tumors. The authors therefore postulated autosomal recessive inheritance of this syndrome, but none of the patients bore offspring to test this hypothesis. A case has recently been reported in which a

family's glioma-polyposis syndrome was inherited in an autosomal dominant fashion.[16] Furthermore, malignant brain tumors have been reported to occur occasionally in families with familial polyposis and Gardner's syndrome, as well as in those with familial nonpolypotic colonic cancer.[12,17] This has led to the more likely conclusion that the glioma-polyposis syndrome is actually a variant of familial colonic cancer syndromes and not a distinct disorder, though the issue has not been entirely settled.[18]

Management

In patients who have familial polyposis coli or Gardner's syndrome cancer of the colon is likely to develop much earlier than in the general population. Fortunately, polyposis develops 10 to 15 years before carcinoma, so that a colectomy can be done before the disease progresses to metastatic malignancy. Polyposis develops in only 5% to 6% of cases before age 20, and the mean age for the detection of the polyps is about 36 years.[4] Our patient presented at age 59, which led his physicians away from the proper diagnosis. One should keep in mind, however, that about 5% of cases present after age 55. No difference in the age of onset or frequency of neoplasia is seen between men and women. Polyps are smaller and the frequency of cancer is much less in patients discovered during the screening of the relatives of an index case, underscoring the value of diligent family screening.

Once the diagnosis of polyposis is made, virtually all patients should be offered colectomy, either total colectomy with abdominoperineal resection or subtotal colectomy with ileorectal anastomosis. Exceptions include adolescents who have not finished growing (in which case the operation may usually be deferred) or patients with metastatic disease, such as our patient, who require only palliative treatment. A complete colectomy is preferred because in a high proportion of patients carcinoma will develop in the rectal segment when it is left behind.[19] In 20% of cases (or less), polyposis does not involve the rectum. These patients tend to be older (median age 58) and usually have negative family histories, suggesting that this may be a clinically distinct subset of polyposis.[19] In the absence of rectal polyposis, the likelihood of rectal cancer developing later is very low and the more limited surgical approach is appropriate. Among patients who have rectal polyposis, however, one initially sees a reduction in the number of polyps following colectomy and ileorectal anastomosis[14] and it was previously assumed that fulguration of the remaining polyps would be adequate management. However, after 20 or more years of follow-up, invasive rectal cancer has developed in a majority (59%) of these patients.[19] For this reason, in most cases of colonic polyposis a proctectomy should be done in concert with one of the newer continent ileostomies.

Unresolved Problems

Several persistent and unresolved problems continue to frustrate the long-term management of these patients. Fulminant desmoid tumors may occur; therapy of these lesions has been disappointing, though some benefit has been reported both with drugs affecting the turnover of adenosine 3′:5′-cyclic phosphate (theophylline and chlorothiazide) and radiation therapy.[7] Gastric lesions include adenomas and a variety of nonneoplastic lesions. These do not seem to require prophylactic surgical management. Small intestinal lesions are far more troublesome because carcinoma (particularly periampullary) is seen in both syndromes,[10,11,20] surveillance of this region is difficult and a prophylactic operation is unreasonable. A number of polypoid lesions have occurred at ileostomy sites, including lymphoid nodules, adenomas and carcinoma.[21] Finally, diligent screening of the relatives of proband cases and genetic counseling are critical procedures that follow the identification of an index case.

TABLE 5.—*Familial Colonic Cancer Without Polyposis*

Characteristic Features
Colonic cancer at an unusually early age risk begins in the third decade peak risk in the fourth and fifth decades
Multiple primary colonic cancer (synchronous and metachronous)
Autosomal dominant inheritance
Increased tendency for cancer in the proximal colon
Increased frequency of mucoid (colloid) cancer[23]
Discrete polyps, but not polyposis, may precede the cancers

From Lynch et al.[22]

Familial Colonic Cancer Without Antecedent Polyposis

CASE 2. Our second patient, a 38-year-old man, had a pulmonary embolus. On physical examination, guaiac-positive stools and a possible rectal mass were noted. A carcinoma at the rectosigmoid junction was reported at sigmoidoscopy and the patient then underwent a successful resection of a Duke's B adenocarcinoma. The family history was that colonic cancer had occurred in 5 of the patient's 11 siblings. Review of the pathologic reports confirmed the diagnosis of cancer in each case. In addition, the patient's father had had colonic cancer and another sibling had had a brain tumor, but pathologic records were unavailable for documentation. The average age for the diagnosis of colon cancer in this family was 39 years. Two of the six documented colonic cancers occurred in the cecum or ascending colon, and the other four were in the distal colon. No family member had colonic polyposis or stigmata of Gardner's syndrome.

The disease illustrated by this family is that of familial colonic cancer in the absence of polyposis (Table 5).[22] The trait is apparently inherited in an autosomal dominant manner in these families. Cancer may occur in the third decade, and the risk rises through the fourth and fifth decades of life. Multiple primary carcinomas may be found at the time of initial diagnosis (synchronous); if part of the colon is not

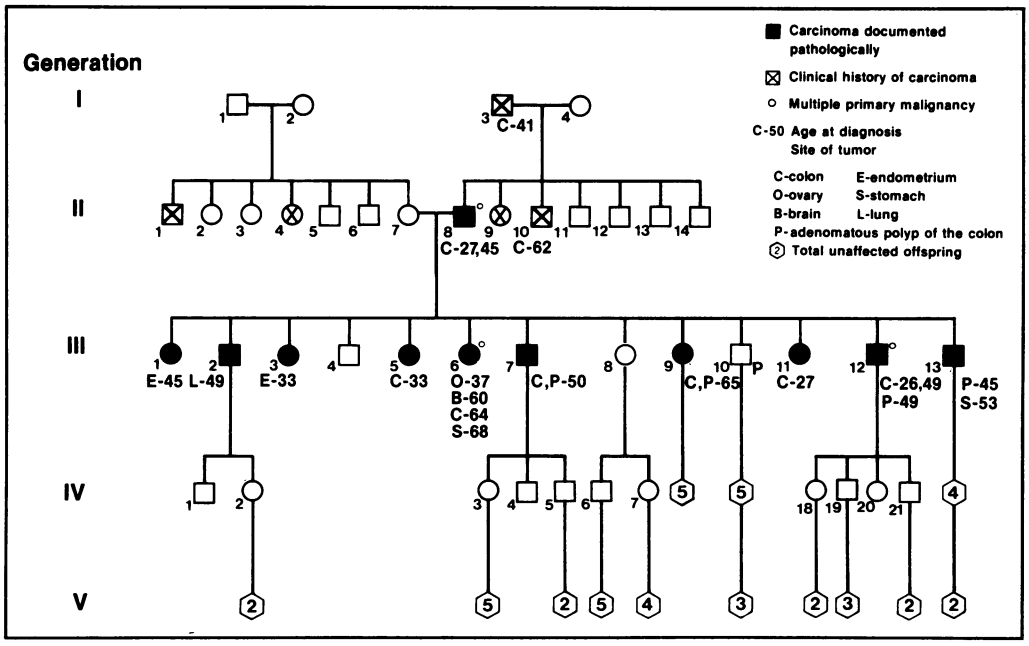

Figure 5.—The family tree from the patient (case 3) with cancer family syndrome. Affected members are found in generations I, II and III; members of generations IV and V are still young.

removed initially, there is a very high likelihood that cancer will recur (metachronous). Recently Lynch[22] has reported an increase in the tendency for cancer to occur in the proximal colon—that is, cecum, ascending or transverse colon—and a rise in the frequency of mucoid or colloid cancer has been reported in this setting.[23] Adenomatous polyps but not diffuse polyposis are often found in the colons of affected persons.

Cancer Family Syndrome

CASE 3. The proband, a 49-year-old man, presented with a recurrent colonic carcinoma in the transverse colon 23 years after a cancer had been removed from the cecum (Figure 5, III-12). No fewer than 12 malignant disorders have occurred among 9 of the patient's siblings. Cancer of the colon occurred in the two prior generations. As shown in the pedigree, carcinoma of the endometrium, ovary, stomach, brain and lung has also occurred in this family. Of significance, three additional cases of cancer have appeared (in III-6, III-9 and III-13) since this family was first worked up and the case was reported in 1978.[24] Carcinoma has not been reported in generations IV and V, most of whom are not yet old enough to have reached maximal risk.

The constellation of cases of familial cancer of the colon, female genital tract and other sites has been called "cancer family syndrome" by Lynch, who has reported on several such families.[25,26] These families suffer from all of the cancer risks described in the previous familial colonic cancer syndrome, including early age of onset, multiple primary malignant lesions, colloid cancer and a predilection for cancer of the proximal colon. These patients are at additional risk for adenocarcinoma at other sites throughout the body. The patients do not have antecedent colonic polyposis, but typically may have one or more adenomatous polyps of the colon, as is shown in case 3 (Figure 5). After the colon, the female genital tract (specifically, endometrium and ovary) is at greatest risk for cancer, again occurring one to two decades earlier than that seen in the general population.

Cancer family syndrome has been reported in at least a dozen well-defined kindreds, but is probably more common than currently appreciated. Recognition of the disease is hampered by the absence of any clear marker and the difficulty of making this diagnosis in any small kindred. Lynch has reported the case of one family consisting of 650 members over six generations.[25] The family was first reported on by Warthin in 1913[27] and described in the literature subsequently in 1925,[28] 1936[29] and 1971.[25] The offspring of the affected members of the original sibship continue to be at very high risk for cancer, whereas the descendants of the unaffected siblings have not suffered an unusual incidence of cancer. Colonic cancers have frequently occurred in the third decade in these patients and occasionally in the teens. In the family of case 3, one can find the first incidence of colonic cancer in persons as young as 26 years of age and as old as 65 years, which adds to the burden of surveillance in such families.

Management

Management of the cases of colonic cancer syndrome without polyposis is more difficult than of those with polyposis because there are no markers of premalignant disease. Once the diagnosis is made, one is advised to remove as much of the colon as possible because the entire colon is at very high risk for recurrent tumor. A reasonable compromise in a patient refusing ileostomy is a subtotal colectomy, ileorectal anastomosis and twice-a-year proctoscopy. The risk of an unresectable rectal cancer developing under this management scheme has not been assessed, and it is not possible to predict whether these patients will behave more like those who

have rectal polyposis (who have a poor outcome when the rectum is spared) or like those who do not have rectal polyposis, as discussed previously. Women who are past childbearing age should be advised to undergo removal of the uterus and ovaries at the time of laparotomy. The risk of carcinoma at other sites is not predictable, and prophylactic removal of other organs is not recommended. It is imperative to seek the appropriate relatives for screening when such a person is identified. Offspring of patients who have this disease should begin having periodic surveillance for cancer between the ages of 20 and 25. Testing of stool specimens for occult blood should be done at least once a year (using the standard series of guaiac-impregnated slides, testing two fecal specimens on three consecutive days during which the patient is ingesting a high-fiber, meat-free diet and avoiding drugs such as aspirin, iron or vitamin C, which may produce spurious results). The patients should then undergo a colonoscopy by age 25, to be repeated every two to three years thereafter if negative. If a single adenomatous polyp is encountered, the surveillance should increase to an annual basis. Women should have an annual aspiration cytologic study of the uterus beginning at age 30 as long as childbearing is planned. Surveillance for cancer at other sites relies primarily on careful history taking, physical examination and a high index of suspicion. Lynch and co-workers have emphasized the difficulty encountered when attempting to encourage asymptomatic family members to undergo a diagnostic evaluation because of the problems of fear, complex mythologies concerning cancer and the role of denial in these families.[5]

Other Syndromes

It has recently been reported that typical features of Muir's syndrome (also known as Torre's syndrome), which consists of a group of unusual cutaneous neoplasms (multiple sites of keratoacanthoma, sebaceous adenoma and carcinoma, basal cell and squamous cell carcinoma) in association with a variety of internal neoplasms (including colonic polyps and cancer), have occurred in otherwise representative cases of cancer family syndrome.[30] Because Muir's syndrome is quite rare, the description of a large kindred over several generations or the identification of an objective marker of disease will be necessary to determine whether Muir's syndrome is actually a variant form of cancer family syndrome.

Second, several kindreds, well described in the literature, show an increased incidence of adenomatous polyps (but not polyposis) and colonic cancer. The increased risk for colorectal neoplasia is inherited as if it were an autosomal dominant characteristic with incomplete penetrance.[31,32] The age that polyps and cancer develop, however, is similar to that seen in the general population—that is, not precocious as in the syndromes discussed above—suggesting that the disorder in these families represents a distinct entity.

TABLE 6.—*Increased Tetraploidy in Cultured Skin Cells*

Potentially a marker of certain familial colonic cancer syndromes	
>7% of cultured cells appear to be tetraploid in:	
7/97	control subjects (range, 15%-19% of cells tetraploid)
66/67	Gardner's syndrome patients (range: 9%-35% of cells tetraploid)
5/33	familial polyposis coli patients (range: 8%-14% of cells tetraploid)
0/2	"Glioma-polyposis" patients
5/5	Non-polypotic familial colonic cancer patients
11/26	Offspring of patients with non-polypotic familial colonic cancer

From Danes.[40]

Mechanisms of Disease

In the past five years there has been a dramatic growth of interest in these syndromes. A better understanding of the mechanisms involved in familial colonic cancer will not only illuminate the general problem of carcinogenesis, but may also lead to the identification of premorbid markers of disease. There are still no reliable and easily carried out tests that can be applied to the offspring of such patients to target those who require careful cancer surveillance and to aid in genetic counseling. Several current lines of investigation, however, promise to help in these areas (Table 6).

Aberrant Proliferation of Colonic Epithelium

Deschner has reported abnormal proliferative patterns in the colonic epithelium of patients who have polyposis.[33] In normal colonic mucosa, cell proliferation and new DNA synthesis occur in the lower two thirds of the crypt of Lieberkühn, whereas these processes are repressed in the differentiated cells of the upper colonic crypt. In the flat colonic mucosa of patients who have polyposis, actively proliferating cells may be found in the upper portion of the crypt and in the surface epithelium, indicating a loss of the normal control of growth and proliferation. This lesion may be found at many grossly normal-appearing sites in the colons of polyposis patients and is also found in adenomatous polyps. The earliest neoplastic lesion may be one of inappropriate DNA synthesis and cell proliferation in the upper portion of the colonic crypt, followed in time by the accumulation of these cells and the development of a mass lesion.

Abnormal Growth of Skin Fibroblasts in Culture

Kopelovich and colleagues have reported that cultured skin fibroblasts from patients with familial polyposis coli and Gardner's syndrome display anomalous behavior in monolayer culture.[13] The growth of normal skin fibroblasts is dependent on the presence of serum (typically 15% of the culture medium) and cell density; growth slows or ceases under conditions of reduced serum concentration or at saturation. In contrast, fibroblasts from patients with polyposis continue to grow in 1% serum and do not exhibit normal con-

tact inhibition when confluency is achieved. Additionally, the intracellular actin matrices are abnormal, and the cells synthesize increased amounts of plasminogen activator. These four characteristics are more typical of tumor cells than normal cells, but such fibroblasts do not fulfill the criteria for bona fide malignant transformation because they still require anchorage to a support medium for growth and do not form tumors when injected into nude mice. Kopelovich and associates have shown, however, that these cells are highly susceptible to neoplastic transformation. After exposure to oncogenic virus, fibroblasts from polyposis patients are 100 to 1,000 times more susceptible to transformation than normal cells, and at least partial transformation may be achieved by the addition of tumor promoter to the culture medium.[34] After such "transformation" the cells may grow transiently in soft agar (anchorage-independent growth) and in some cases give rise to tumors when injected into the anterior chamber of the eye of a nude mouse. Other laboratories have confirmed the abnormal growth characteristics and increased susceptibility to viral transformation,[35] and it has been observed that these cells display higher susceptibility to transformation after exposure to alkylating agents.[36,37] Some questions remain, however, concerning the effects of tumor promoters and further confirmation is required on this issue.[38] By all appearances, therefore, fibroblasts from normal skin of polyposis patients behave as if they were "initiated" and are highly susceptible to malignant transformation. This is a promising avenue for the identification of presymptomatic carriers of the polyposis genes, though these techniques are still under development and are not yet widely available for diagnostic purposes.

Chromosomal Aberrations

A number of abnormalities in the chromosomes of lymphocytes or fibroblasts have been observed in patients with Gardner's syndrome and familial polyposis coli, suggesting generalized nuclear instability in these syndromes. The most consistent defect has been seen in chromosome 2, but a variety of random losses and gains of single chromosomes have been reported by Gardner and co-workers.[39]

Increased Tetraploidy in Cultured Skin Cells

Perhaps germane to the above discussions, Danes[40] has reported chromosomal abnormalities in cultures of skin biopsy specimens that possess both fibroblasts and dermal epithelial cells from patients with certain of the inherited colon cancer syndromes. After growth for 6 to 12 weeks in monolayer culture, cells were prepared for examination of mitotic figures. A higher percentage of tetraploid mitosis was seen in the cultures from patients with polyposis than from the controls. The results have been expressed as the percentage of metaphase cells exhibiting in vitro tetraploidy (Table 7). A group of controls (from whom no history of colonic cancer was obtained) was studied, and in 93% of them 0% to 7% of the mitosis was tetraploid, establishing a "normal" range. Only 3% of the controls had more than 9% tetraploidy. Among patients with Gardner's syndrome, 99% had increased in vitro tetraploidy. Among family members who were "at risk" from the families with Gardner's syndrome, 20% showed increased tetraploidy. Curiously, only 15% of patients with familial polyposis coli showed increased tetraploidy, and only 15% of the familial polyposis coli family members "at risk" had this abnormality. Of note, a total of six progeny were studied from the patients with familial polyposis coli, who themselves showed over 7% tetraploidy, and half were abnormal, in contrast with none of the offspring of index patients with familial polyposis coli who had less than 7% tetraploidy. Therefore, this technique appears to identify in vitro an inherited abnormality in most patients who have Gardner's syndrome, in a few of the patients with familial polyposis coli and in a subset of offspring who are "at risk" but in whom polyposis or cancer has not yet developed.

TABLE 7.—*Mechanisms Postulated for Familial Colonic Cancer and Cancer Family Syndrome*

Defective recognitive immunity; impaired response in mixed leukocyte culture[41]
Excessive suppressor macrophages
Various chromosomal aberrations[42,43]
Impaired immune response[42]

Perhaps the most promising aspect of Danes' work is the preliminary finding in patients with familial colonic carcinoma syndromes without polyposis.[40] Of five patients studied thus far, all show excess tetraploidy, and 42% of the family members at risk showed the same abnormality. This unexpected finding identifies a biologic link between the colonic cancer syndromes with and without polyposis, and is possibly a marker for premorbid disease in the latter group. However, these techniques have not been attempted in other laboratories and require additional investigation and confirmation.

Immunologic Abnormalities in the Familial Nonpolypotic Colonic Cancer Syndromes

Much of the investigation into the mechanisms underlying the familial colonic cancer syndromes in the absence of polyposis has focused on dysfunction of the immune system. Berlinger and colleagues[41] have reported a decrease in the responsiveness of lymphocytes to allogenic stimuli in mixed leukocyte culture in three of five such persons. Unfortunately, the other two did not have this abnormality. Also, one of the three who had the defect also had metastatic cancer, and hyporesponsiveness to this type of allogenic stimulation had previously been observed by these authors in persons who had established malignant lesions. It is of great interest that when a group of the healthy first-degree relatives of these patients at risk for the familial cancer syndrome was tested, 8/18 (42%) were found to have the same defect in mixed leukocyte culture. None of 13 persons with familial polyposis coli showed this lack

of immune responsiveness, whereas both patients with Gardner's syndrome were hyporesponsive, again linking Gardner's syndrome pathophysiologically with the nonpolypotic colonic cancer syndromes, as did Danes' work.

Law and associates[42] have reported impaired blastogenic responses to in vitro mitogens in patients with the familial nonpolypotic cancer syndromes and in a proportion of their healthy progeny. Other defects such as impaired skin reactivity to an allogenic tumor antigen and a relative decrease in E-rosette-forming cells were reported in these patients. From a clinical perspective, the scope of the immune deficit must be very selective because affected members in these families do not have other manifestations of immunodeficiency such as unusual infectious complications, and when the tumors are detected and resected at an early stage, long-term survivals are not uncommon. Thus, the significance of these in vitro observations should not be overinterpreted.

Chromosomal Aberrations in the Familial Nonpolypotic Colonic Cancer Syndromes

One final line of investigation has suggested the presence of a variety of chromosome abnormalities in the familial nonpolypotic colonic cancer syndromes. Law and co-workers[42] have reported the occasional occurrence of ring and dicentric forms as well as breaks and fragmentation of chromosomes in affected and nonaffected at risk family members. A very promising development in this area has been the identification of a possible animal model of familial colonic cancer in a South American primate,[43] in which a high rate of spontaneous colonic cancer occurs. Cytogenetic analysis of cultured lymphocytes has indicated an increased susceptibility to mitomycin C-induced chromosomal damage in these animals. If this model should prove appropriate, it could greatly enhance our understanding of the genetically determined susceptibility to cancer of the colon.

Summary

A clinical overview of the familial colonic cancer syndromes has been presented. Those syndromes that are characterized by antecedent colonic polyposis are well known to most clinicians. It has become clear that familial polyposis coli, Gardner's syndrome and the variants of both overlap extensively and represent the multiple clinical faces of a single disease. Research into the underlying mechanism of disease has found abnormalities in the growth characteristics of colonic epithelium in vivo and of cultured skin fibroblasts in vitro. These lines of investigation appear to be leading to a means of making the diagnosis before the first adenoma develops.

The familial colonic cancer syndromes in the absence of polyposis (site-specific colon cancer and the cancer family syndrome) are less well known to most clinicians and may be very difficult to recognize because of the absence of reliable markers of this disease. Research into these syndromes has thus far focused on defects in the immune system and chromosomal abnormalities (Table 7). Preliminary work on cultured skin tissues from a small number of patients has indicated the presence of the same in vitro aberration seen in patients with Gardner's syndrome, suggesting common ground between the polypotic and nonpolypotic syndromes.

The challenge with all of these patients is simple. If one can identify these syndromes before the development of metastatic cancer, patients and their families will be well served. One must only think of the possibility of familial cancer, find the disease early in its natural history and enlighten the appropriate family members of their risks. These syndromes are a challenge to clinicians, and offer investigators an opportunity for further insight into the nature of human cancer.

QUESTIONS AND ANSWERS

DR THOMAS BOYER: *Will in vitro testing of skin fibroblasts be adequate to help counsel patients at risk for familial colonic cancer who are going to be married?*

DR BOLAND: The abnormality in skin fibroblasts has occurred only in patients who have polyposis, who are somewhat easier to identify in the premalignant state because polyps often develop by the time they are in their 20s or 30s. But in a substantial number of those who carry the gene polyps will not develop until later on, and Kopelovich is still cautious in stating that he can definitely detect those asymptomatic persons who carry the gene. He and Gardner have recently published findings suggesting that the cloning efficiency of skin fibroblasts and their response to tumor promoter are promising modalities for screening progeny who are at risk to carry the gene.[44] These tests are not yet widely available, however, and remain primarily research tools. The current projection is that a battery of in vitro tests will be the most sensitive way to identify gene carriers. Ideally, a few centers would be established to support and evaluate these tests.

DR SMITH: *How young have patients been who have been tested in this manner? Is this predictive even in children?*

DR BOLAND: Teenagers and children as young as age 5 have been tested, and the characteristic has appeared even at this young age. However, it will require time to determine how accurate the test is, since most of the young persons at risk who have been tested have not been followed long enough to determine if they actually have the disease. This characteristic therefore appears at a very early age and may be congenital.

DR ROBERT OCKNER: *Were the maturational abnormalities of colonic epithelium also seen in the younger patients?*

DR BOLAND: As with the abnormalities in skin fibroblasts, these changes have also been seen in younger persons (teenagers), antedating the development of

polyposis. It is not known whether this lesion is present from birth. The problem again arises that the progeny tested for this characteristic must be followed long enough to establish presence or absence of the gene before the predictive value of the finding may be evaluated.

DR RICHARD WEISIGER: *A number of oncogenic viruses have been found to contain a single "cancer gene," a form of which is also present in normal genomes. Is there any evidence that an abnormal regulation or dosage of such a gene may be involved in any of these familial syndromes?*

DR BOLAND: This avenue of investigation is only beginning to receive attention. The only study I am aware of has used a single oncogene probe and did not find any evidence to link an abnormality in the expression of that oncogene to familial colon cancer. However, this very fertile topic has yet to be explored in any depth.

DR SMITH: *We have in our audience an expert in the oncogene field, Dr Harold Varmus, who along with Dr Michael Bishop, recently won the Lasker Award for his work with oncogenic viruses. Would you like to comment on this, Dr Varmus?*

DR VARMUS:* I have one comment about recent efforts to identify the gene involved in Gardner's syndrome, and the chromosome on which that gene resides. DNA that is obtained from cultured colonic carcinoma cells may be applied to normal 3T3 mouse cells, and the recipient cells sometimes undergo malignant transformation. The gene responsible for that transformation has been identified as the progenitor cellular homologue of a viral transforming gene called the "ras" gene. Dr Raymond White of Salt Lake City, who has access to some of the large Gardner's syndrome families, has shown by analysis of genetic polymorphisms that the mutation in Gardner's syndrome is not closely linked to the gene identified by the DNA transformation studies. So, it is not the *ras* gene that is involved in Gardner's syndrome.

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